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Aluminium(III) halides mediated synthesis of 5-unsustituted 3,4-dihydropyrimidin-2(1*H*)-ones *via* three component Biginelli-like reaction

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5-Unsubstituted-3,4-dihydropyrimidin-2(1*H*)-ones have been synthesized in excellent yields in a aluminium(III) halides mediated three component cycloaddition of aldehyde, urea and enolizable ketone.

Keywords: Aluminium(III) halides, enolizable ketone, aldehyde, urea, 5-unsubstituted-3,4-dihydropyrimidin-2(1*H*)-one

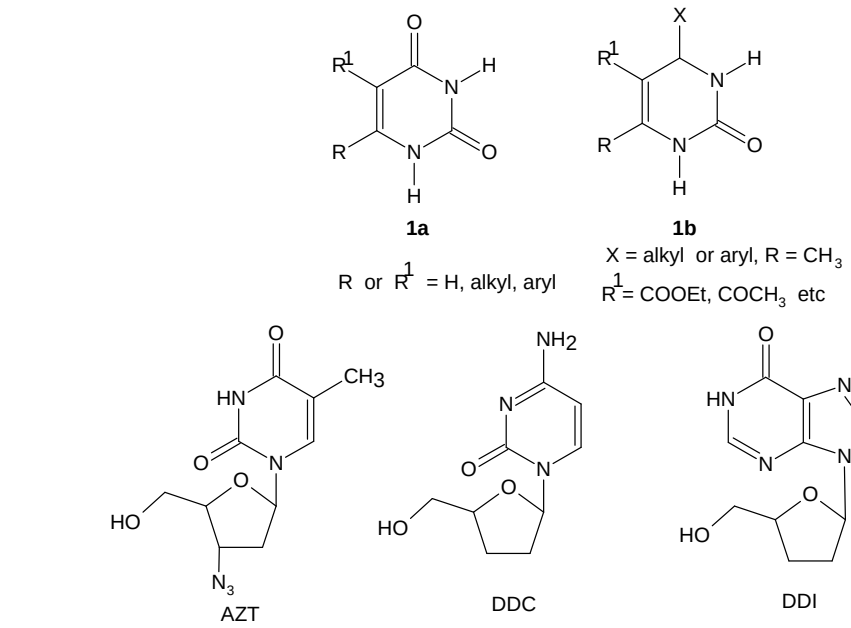
Multicomponent condensation reactions (MCRs) have recently emerged as powerful tools in organic synthesis. This is necessitated for fast library development of biologically significant organic compounds *viz* to achieve diversity quickly by simply varying each component[1]. MCR has become indispensable in view of the high throughput screens (HTS) available for fast screening of biologically significant compounds. Historically, the earliest MCR was the Strecker reaction[2] which dates back to 1850 and other subsequent reactions[3]. The biological significance of pyrimidines is well established as this scaffold has been positioned as a privileged molecule *i.e.* having a wide spectrum of biological activity like antiviral[4], anticancer[5] and several others[6]. The clinically important antiretroviral agents like AZT, DDC, DDI (**Scheme I**) possess the pyrimidine **1a** scaffold. Another related framework of the **1b** type is also very easily accessible *via* MCR involving urea, active methylene compounds and aldehydes in the presence of a catalyst as originally reported[7] by Biginelli. In recent years, type **1b** pyrimidine scaffold has been under intensive investigation[8] as it has a very broad pharmacological profile such as calcium channel blockers[9], antihypertensive agents[10] (these can be considered as aza-analogues of clinically used drugs[11] like niguldipine, felodipine, nifedipine) and alpha-1a-antagonists[12].

Certainly, this very promising biological profile bodes well for **1b** type of framework. Because of these activities several novel and efficient methods are known for the production of Biginelli scaffold. In most of these new methods, a variety of Lewis acid catalysts such as $CuSO_4$ (Ref. 13a), $TiCl_4$ (Ref. 13b), $ZnCl_2$ (Ref. 13c), rare earth triflates[13d], LiBr (Ref. 13e), $InCl_3$ (Ref. 13f), $InBr_3$ (Ref. 13g), $SnCl_2.2H_2O$ (Ref. 13h), *etc.* have been employed. In all these reported procedures the major focus has been on the development of new and efficient catalyst systems and a majority of these developments proved to be quite fruitful and skeletal changes were somewhat ignored.

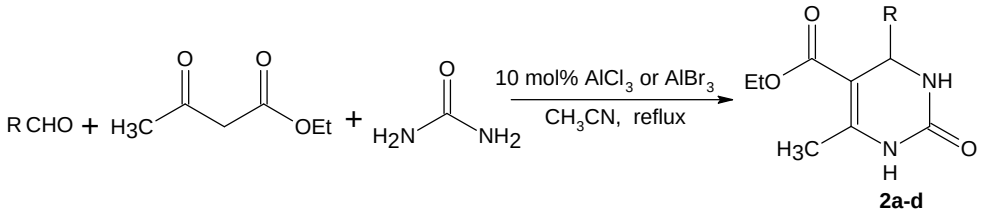
The chemistry of C_5-C_6 double bond has been extensively explored in type **1a** skeleton and careful manipulation of this bond have led to interesting chemistry[14] and many useful new structures. In contrast, C_5-C_6 double bond in Biginelli scaffold is relatively less explored and only a few useful transformations are attempted[15] involving very careful multistep manipulations. This less developed chemistry of C_5-C_6 bond in Biginelli compounds appears to be due to the difficulties in manipulating the methyl group at C_6 and ester group at C_5 which are traditionally placed in these positions.

Of course, there are sporadic reports[16] of the production of C_5 unsubstituted compounds. These involve complex multistep procedures. For example, one reported procedure involves careful saponification and thermal decarboxylation which is most certainly a low yielding drastic step and not at all a practical procedure. Another procedure[16e] starting from ketocarboxylic acids is equally unattractive.

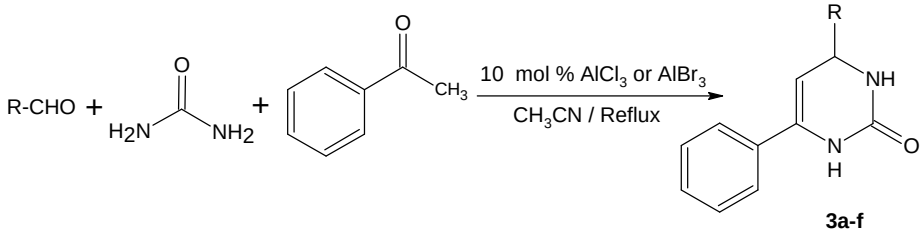
In continuation of the work on both the systems *viz* **1a** and **1b**, herein is reported the results of the current investigations on the facile one pot synthesis of 5-unsubstituted-3,4-dihydropyrimidin-2(*1H*)-ones which involve the use of enolisable ketones (**Scheme II**) like



Scheme I



Scheme II



Scheme III

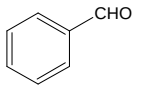
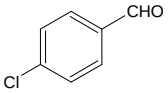
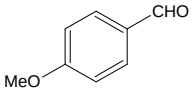
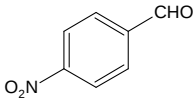
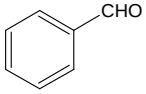
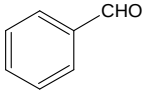
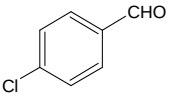
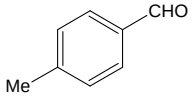
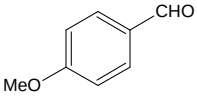
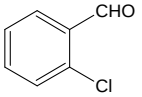
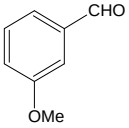
acetophenone instead of 1,3-dicarbonyl compounds[17] as in the case of classical Biginelli reaction and Al(III) halides (**Scheme III**).

Initial studies on the traditional Biginelli reaction with this catalyst system (**Scheme II**) proceeded very smoothly affording high yields (**Table I**, entry 1-4). After this initial success, the same conditions were applied to the combination of enolizable ketone[18], urea and aldehydes to obtain the desired products in excellent yields (**Table I**).

In a typical experimental procedure, to a mixture of acetophenone (600 mg, 5.0 mmol) and $AlCl_3$ (10 mol%) in CH_3CN (25 mL) was added benzaldehyde (530 mg, 5.0 mmol) and urea (450 mg, 7.5 mmol) with stirring. The resulting mixture was refluxed for 6 hr. After completion of reaction (as followed by TLC), excess acetonitrile was evaporated under reduced pressure. The residue was treated with cold water (30 mL). The crude product thus obtained was filtered and purified by recrystallization from ethanol to afford 3,4- dihydro-4,6-diphenylpyrimidin-2(1*H*)-one **3a** in 90% yield, m.p. 233-36°C. The spectral

characterization data fully supports the assigned structure[19], as shown in the experimental section.

Table I — Al(III) halides mediated synthesis of 3,4-dihydropyrimidin-2(*1H*)ones and 5-unsubstituted 3,4-dihydropyrimidin-2(*1H*)ones

Entry	Aldehyde	Products[a]	Time (hr)	Yield[b] (%)	m.p. (°C)
1		**2a**	5	92	201-02
2		**2b**	4.5	94	212-13
3		**2c**	5	91	200-01
4		**2d**	4.5	90	208-10
5		**3a**	6.0	90	233-36
6			15.0	0[c]	
7		**3b**	6.0	92	267-69
8		**3c**	6.5	86	248-50
9		**3d**	6.5	84	259-61
10		**3e**	6.0	91	260-63
11		**3f**	7.0	88	256-58

[a] All compounds thus obtained were characterized by comparison of physical and spectral data with authentic samples.
[b]yields refer to pure isolated product.
[c]at RT.

The other 5-unsubstituted 3,4-dihydropyrimidin-2(*1H*)ones were similarly prepared in excellent yields by following the same procedure. The structures of all the products thus obtained were fully characterized using physical and spectral techniques. It is pertinent to mention here that comparable results were obtained when $AlBr_3$ was employed in this reaction instead of $AlCl_3$ (**Table I**).

The probable mechanism of the reaction appears to involve the activation of the carbonyl function by $AlCl_3$, thereby making the methyl group readily enolisable, which in turn reacts with aldehyde and urea derived imine in a Michael type step to produce product **3**. This view is further substantiated when TMSI is found to show some improvement in yields which is an established carbonyl activating group.

Indeed, this investigation could be extended to a cyclic ketone like cyclohexanone as shown in **Scheme IV**.

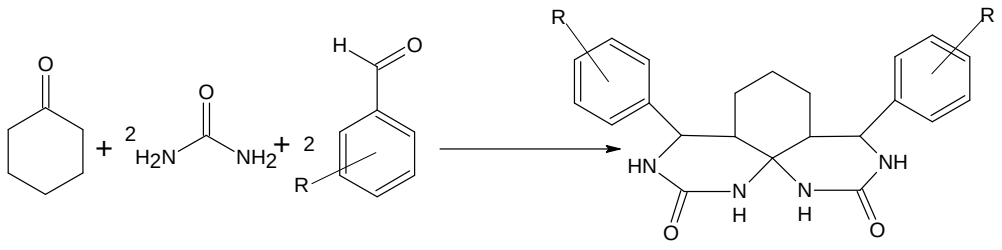
In a typical example, to a mixture of cyclohexanone (490 mg, 5.0 mmol) and $AlCl_3$ or $AlBr_3$ (10 mol%) in CH_3CN (25 mL) was added benzaldehyde (1.06 g, 10.0 mmol) and urea (900 mg, 15.0 mmol) with stirring. The resulting mixture was refluxed for 6 hr. After completion of reaction (as followed by TLC), excess acetonitrile was evaporated under reduced pressure. The residue was treated with cold water (30 mL). The crude product thus obtained was filtered and purified by recrystallization from ethanol to afford **4a** in 92% yield, m.p. 328-30°C (entry 1, **Table II**). Similarly, other aldehydes were reacted following the same procedure affording the spirofused heterotricyclic products in 85-92% yield (**Table II**).

For in-depth study and to evaluate the catalytic efficacy of various Lewis acids in this reaction, some other combinations have been tried (see **Table III**). As is clear from the data given in **Table III**, $AlCl_3$ and $AlBr_3$ appear to be the most effective. Rest of the combinations are either not very good or ineffective. For example, $FeCl_3$ or $AlBr_3$ produce some significant results but not better than the $AlCl_3$ and KI system. When $FeCl_3.6H_2O$ is utilized, the reaction is rather complicated and the desired product is not obtained. So is the case with $AlCl_3.6H_2O$. When trimethylsilyl iodide is used, the yields did not improve significantly but this still seems to be a good additive.

To conclude, the present investigation describes a simple, facile and efficient one pot protocol for the synthesis of 5-unsubstituted 3,4-dihydropyrimidin-2(*1H*)ones utilizing readily available and cheap commercial chemicals.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. Reagent grade chemicals were purchased from commercial sources and used as

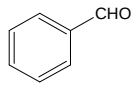
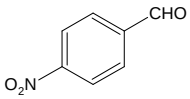
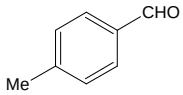
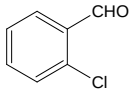


4a-d

Scheme IV

received. IR spectra were recorded in KBr discs on a Perkin-Elmer 24OC analyzer. ^{1}H NMR spectra were recorded on a Varian Gemini 300 (300 MHz) spectrometer using TMS as internal standard. The progress of reaction was monitored by TLC using silica gel G (Merck).

Table II — Al(III) halides mediated reaction of cyclohexanone, aldehydes and urea

Entry	Aldehydes	Products[a]	Time (hr)	Yield[b] (%)	m.p. (°C)
1		**4a**	6	92	328-30
2		**4b**	6	85	342-45
3		**4c**	6.5	88	349-52
4		**4d**	6	89	322-24

[a]Products are characterized by m.p. and spectral technique.
[b]Isolated yields

Table III — Synthesis of 3,4-dihydro-4,6-diphenylpyrimidin-2(1*H*)-one **3a** in presence of 0.5 mmol of different catalysts[a]

Entry	Catalyst	Time (hr)	Yield (%)
1	$FeCl_3$	26	45
2	$FeCl_3$ + KI	19	62
3	$FeCl_3.6H_2O$+KI	10-12	n.r.
4	$AlCl_3.6H_2O$	16	n.r.[b]
5	$AlCl_3$	6	92
6	$AlBr_3$	6	91
7	$AlCl_3$ + TMSI	6-7	90

[a]Acetophenone (5 mmol), urea (7.5 mmol), aldehyde (5 mmol) and 10 mol % of catalysts
[b]Negligible/no reaction

General procedure for the synthesis of 5-unsubstituted 3,4-dihydropyrimidin-2(*1H*)ones 3a-f: To a mixture of acetophenone (5.0 mmol) and $AlCl_3/AlBr_3$ (10 mol%) in CH_3CN (25 mL) was added aldehyde (5.0 mmol) and urea (7.5 mmol) with stirring. The resulting mixture was refluxed for the required duration (**Table I**). After completion of reaction (as monitored by TLC), excess acetonitrile was evaporated under reduced pressure. The residue was treated with cold water (30 mL). The crude product thus obtained was filtered and purified by recrystallization from ethanol to afford 5-unsubstituted 3,4-dihydropyrimidin-2(*1H*)ones in 84-92% yield.

General procedure for the reaction of cyclohexanone, aldehydes and urea: To a mixture of cyclohexanone (5.0 mmol) and $AlCl_3/AlBr_3$ (10 mol%) in CH_3CN (25 mL) was added aldehyde (10.0 mmol) and urea (15.0 mmol) with stirring. The resulting mixture was refluxed for the required duration (**Table II**). After completion of reaction (as monitored by TLC), excess acetonitrile was evaporated under reduced pressure. The residue was treated with cold water (30 mL). The crude product thus obtained was filtered and purified by recrystallization from ethanol to afford the desired spirofused heterotricyclic products in 85-92% yield.

Selected spectral data

Compound **2a**: m.p. 201-02°C; IR (KBr): 3412, 3229, 1710, 1639 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 9.18 (s, 1H), 7.73 (s, 1H), 7.20-7.30 (m, 5H), 5.14 (s, 1H), 3.98 (q, *J*=7.2 Hz, 2H), 2.24 (s, 3H), 1.06 (t, *J*=7.2 Hz, 3H).

Compound **2d**: m.p. 208-10°C; IR (KBr): 3415, 3236, 1715, 1675 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 9.28 (s, 1H), 8.26 (d, *J*= 8.7 Hz, 2H), 7.80 (s, 1H), 7.70 (d, *J*=8.7 Hz, 2H) 5.26 (s, 1H), 3.93 (q, *J* =7.0 Hz, 2H), 2.25 (s, 3H), 1.09 (t, *J* =7.0 Hz, 3H).

Compound **3a**: m.p. 233-36°C; IR (KBr): 3312, 1685, 1598, 1449 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 9.51 (s, 1H, NH), 9.21 (s, 1H, NH), 7.21- 7.62 (m, 10H, Ar-H), 5.20 (d, 1H, *J* = 4.1 Hz, C=CH), 5.12 (d, 1H, *J* = 4.1 Hz, CH).

Compound **3b**: m.p. 267-69°C; IR (KBr): 3319, 1683, 1569, 1463 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.42 (s, 1H, NH), 9.12 (s, 1H, NH), 7.19- 7.78 (m, 9H, Ar-H), 5.60 (d, 1H, J = 4.3 Hz, C=CH), 5.01 (d, 1H, J = 4.3 Hz, CH).

Compound **3d**: m.p. 259-61°C; IR (KBr): 3345, 1645, 1536, 1422 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.23 (s, 1H, NH), 8.87 (s, 1H, NH), 7.18- 7.56 (m, 9H, Ar-H), 5.85 (d, 1H, J = 5.6 Hz, C=CH), 5.26 (d, 1H, J = 5.6 Hz, CH), 3.69 (s, 3H, OCH_3).

Compound **4a**: m.p. 328-30°C; ^1H NMR (DMSO-d_6): δ 7.40-7.19 (m, 10 H), 7.08 (s, 1H), 6.97 (s, 1H), 6.62 (s, 1H), 6.39 (s, 1H), 4.50 (d, 1H), 4.82 (d, 1H), 2.02 (m, 2H), 1.38 (m, 2H), 1.24 (m, 2H), 0.82 (t, 2H).

Compound **4d**: m.p. 322-24°C; ^1H NMR (DMSO-d_6): δ 7.42 (s, 1H), 7.35-7.10 (m, 9H), 6.75 (s, 1H), 5.32 (s, 1H), 5.32 (s, 1H), 3.91 (m, 3H), 3.69 (m, 3H), 2.30 (m, 2H), 2.01 (m, 1H), 1.84 (m, 1H), 1.32 (m, 1H), 1.19 (m, 1H), 0.89 (m, 1H).

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17 As in the classical Biginelli, group at C_6 is always methyl and at C_5 always a substituents like carboxylic acid ester or any other substituents.

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19 Though a variety of conditions were tried, the formation of any isolable product was not encountered. However, formation of valence tautomer of **3** was quite conceivable *via* enamine-imine tautomerism.